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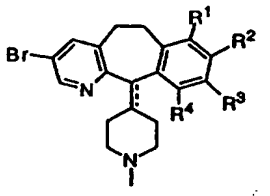
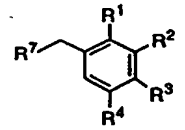
(54) Title: SYNTHESIS OF INTERMEDIATES USEFUL IN PREPARING BROMO–SUBSTITUTED TRICYCLIC COMPOUNDS

(57) Abstract

The invention relates to a process for preparing a compound of formula (I), comprising: (a) reacting 2,5–dibromo–3–methylpyridine with an amine of the formula NHR^5R^6 to obtain an amide; (b) reacting the amide with a compound of formula (3) in the presence of a strong base to obtain a compound of formula (4); (c) converting a compound of formula (4) to the corresponding cyano compound or aldehyde; (d) reacting the cyano compound or aldehyde with a piperidine derivative to obtain an aldehyde or alcohol of formula (7a) or (7b), respectively; (e) cyclizing a compound of formula (7a) or (7b); wherein R^1–R^7 are as defined in the specification.



(I)



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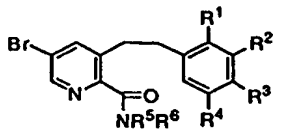

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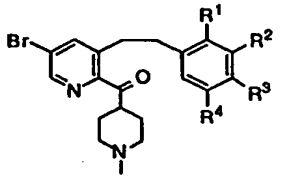
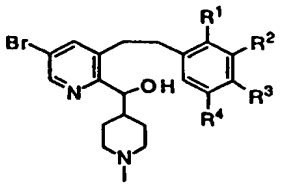


(7a)



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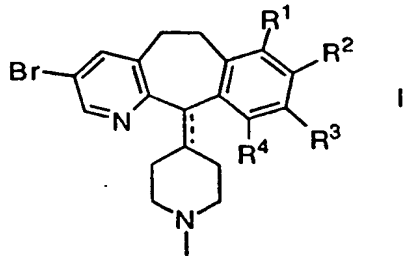
SYNTHESIS OF INTERMEDIATES USEFUL IN PREPARING BROMO-SUBSTITUTED TRICYCLIC COMPOUNDS

BACKGROUND OF THE INVENTION

This invention provides an improved process for preparing intermediates useful in the preparation of bromo-substituted tricyclic compounds known as antihistamines and as inhibitors of farnesyl protein transferase (FPT). In particular, the compounds of this invention are useful in the preparation of antihistamines such as those disclosed in U.S. Patent 5,151,423, and of FPT inhibitors disclosed in International Application No. PCT/US96/19603, filed December 19, 1996.

SUMMARY OF THE INVENTION

This invention provides a process for preparing a compound of the formula



I

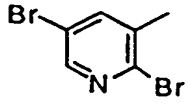
wherein:

R^1, R^2, R^3 and R^4 are independently selected from the group consisting of hydrogen and halo, provided that at least one of R^1, R^2, R^3 and R^4 is hydrogen and at least one of R^1, R^2, R^3 and R^4 is halo; and

the dotted line represents an optional double bond;

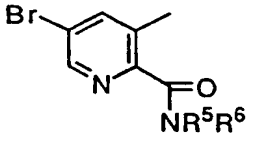
comprising:

(a) reacting a compound of formula 1



1

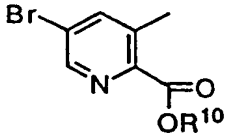
(i) with an amine of the formula NHR^5R^6, wherein R^5 is hydrogen and R^6 is C_1-C_6 alkyl, aryl or heteroaryl; R^5 is C_1-C_6 alkyl, aryl or heteroaryl and R^6 is hydrogen; R^5 and R^6 are independently selected from the group consisting of C_1-C_6 alkyl and aryl; or R^5 and R^6, together with the nitrogen to which they are attached, form a ring comprising 4 to 6 carbon atoms or comprising 3 to 5 carbon atoms and one hetero moiety selected from the group consisting of -O- and $-NR^9-$, wherein R^9 is H, C_1-C_6 alkyl or phenyl; in the presence of a palladium catalyst and carbon monoxide to obtain an amide of formula 2:



2

; or

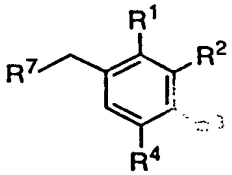
(ii) with an alcohol of the formula $R^{10}OH$, wherein R^{10} is C_1-C_6 lower alkyl or C_3-C_6 cycloalkyl, in the presence of a palladium catalyst and carbon monoxide to obtain the ester of formula 2A



2A

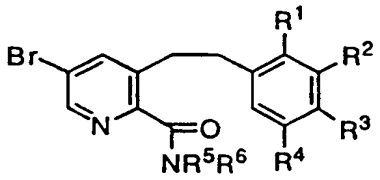
followed by reacting the compound of 2A with an amine of formula NHR^5R^6 to obtain the amide of formula 2;

(b) reacting the amide of formula 2 with a compound of formula 3



3

wherein R^1, R^2, R^3 and R^4 are as defined above and R^7 is Cl or Br, in the presence of a strong base to obtain a compound of formula 4



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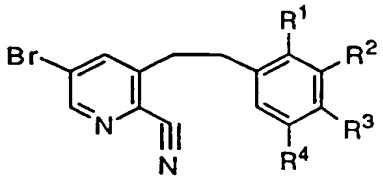
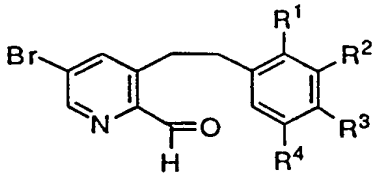
(c)(i) converting a compound of formula 4 to a cyano compound of formula 5a



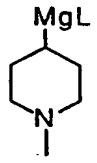
5a ; or

(c)(ii) converting a compound of formula 4 or a cyano compound of formula 5a to an adlehyde of formula 5b



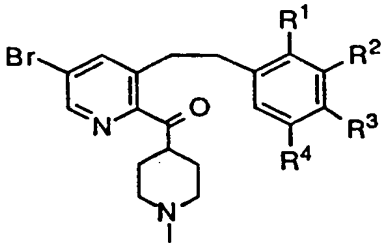
5b

(d) reacting compound 5a or 5b with a piperidine derivative of formula 6

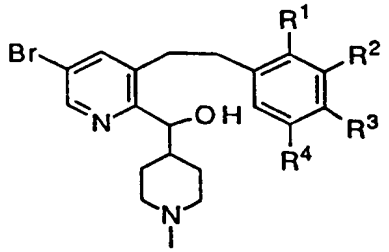


6

wherein L is a leaving group selected from the group consisting of Cl and Br, to obtain a ketone of formula 7a or an alcohol of formula 7b, respectively:



7a



7b

(e)(i) cyclizing a compound of formula 7a to obtain a compound of formula I wherein the dotted line represents a double bond; or

(e)(ii) cyclizing a compound of formula 7b to obtain a compound of formula I wherein the dotted line represents a single bond.

Preferred compounds of formula I are those wherein R^2 is halo. Also preferred are compounds wherein R^1 and R^3 are each hydrogen. Another group of preferred compounds is that wherein R^1, R^3 and R^4 are hydrogen and R^2 is halo. Still another group of preferred compounds is that wherein R^1 and R^3 are each hydrogen and R^2 is halo. Yet another group of preferred compounds is that wherein R^1 and R^3 are each hydrogen and R^2 and R^4 are independently selected from the group consisting of halo. Halo is preferably Cl or Br.

DETAILED DESCRIPTION

As used herein, the term "lower alkyl" means straight or branched alkyl chains of 1 to 6 carbon atoms.

"Halo" refers to fluorine, chlorine, bromine or iodine radicals.

"Aryl" means phenyl, substituted phenyl wherein the substituents are 1 to 3 substituents independently selected from the group consisting of C_1 to C_6 alkyl and C_1 to C_6 alkoxy, benzyloxy or naphthyl.

"Heteroaryl" means a 5- or 6-membered aromatic ring comprising one or two nitrogen atoms, e.g., pyridyl, pyrimidyl, imidazolyl or pyrrolyl.

When R^5 and R^6, together with the nitrogen to which they are attached, form a ring comprising 4 to 6 carbon atoms, the rings so produced are exemplified by pyrrolidinyl, piperidinyl and perhydroazepine. When R^5 and R^6, together with the nitrogen to which they are attached, form a ring comprising 4 to 5 carbon atoms and a heteroatom, the rings so produced are exemplified by piperazinyl, N-methyl-piperazinyl, N-phenyl-piperazinyl and morpholinyl.

The compounds prepared by the process disclosed above are useful as intermediates in the procedures described in PCT/US96/19603 and U.S. 5,151,423 to obtain the desired compounds wherein the piperidinyl ring is N-substituted. By using the 3-bromo-substituted intermediates prepared by the process of this invention, the

desired tricyclic antihistamines and FPT inhibitors described above can be made by an eleven-step process rather than the fifteen-step process disclosed in the art.

Compounds of formula I can be converted to other compounds of formula I by methods known in the art, i.e., compounds wherein R^1, R^2, R^3 or R^4 is hydrogen can be converted to the corresponding compounds wherein R^1, R^2, R^3 or R^4 is halogen. Such procedures are shown in PCT/US96/19603, wherein, for example, a compound wherein R^2 is Cl, R^1, R^3 and R^4 are hydrogen and the piperidinyl nitrogen is protected by a $-COOCH_2CH_3$ group is reacted with KNO_3, the resulting nitro-substituted compound is reduced to the amine, the resulting compound is reacted with Br_2 and the amino group is removed to obtain a compound wherein R^2 is Cl, R^4 is Br and R^1 and R^3 are hydrogen.

In step (a), the di-bromo-substituted pyridine of formula 1 is reacted with the amine NHR^5R^6 in the presence of a palladium catalyst, carbon monoxide (CO) and a base. As defined above, the amines of formula NHR^5R^6 are exemplified by t-butylamine, aniline, N-methyl-aniline, pyrrolidine, piperidine, perhydroazepine, piperazine, N-methyl-piperazine, N-phenyl-piperazine and morpholine. Preferred amines are pyrrolidine and t-butylamine, with t-butylamine being most preferred.

Palladium catalysts are exemplified by $Pd(OAc)_2/P(R^{11})_3$ at ratios of 1:1 or 1:2; $(PPh_3)_2PdCl_2$ at a range of 0.5 to 40 mol%, preferably 1 to 10 mol%, and most prefereably 1 to 5 mol%; $Pd(PPh_3)_4$; $(R^{11})_3P/Pd_2(dba)_3$; $Pd(OAc)_2$/2,2'-bipyridine at ratios of 1:1 to 1:2, preferably 1 to 10 mol%; and Pd/C, wherein Ac is acetyl, R^{11} is C_1 to C_6 alkyl or aryl, Ph is phenyl, and dba is dibenzylidene acetone. Preferred catalysts are $Pd(OAc)_2/P(R^{11})_3$ and $(PPh_3)_2PdCl_2$.

The amount of amine (NHR^5R^6) reacted ranges from 1 to 4 equivalents, and is preferably 1 to 1.5 equivalents. Suitable bases include, but are not limited to, C_1 to C_6 alkyl amines such as triethylamine (Et_3N), t-butylamine and 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU), and inorganic bases such as K_2CO_3, Na_2CO_3, Na_2HPO_4 and NaOH. Preferred bases are K_2CO_3 and Et_3N, with Et_3N being most preferred.

Suitable solvents are tetrahydrofuran (THF), dimethylformamide (DMF), acetonitrile (CH_3CN) and toluene or a combination thereof. CH_3CN is preferred for reaction with an amine and a combination of CH_3CN and toluene is preferred for reaction with an alcohol. The temperature range for the reaction is 35°C to 100°C, preferably about 55°C for reaction with the amine and preferably about 80°C for reaction with an alcohol. The reaction is carried out at a pressure of 5 psi to 500 psi, preferably 40 to 200 psi, and most preferably at 50 to 150 psi. The time for reaction ranges from 2 hours to 4 days, preferably 4 hours to 2 days, and most preferably 16 to 48 hours.

Conversion of the ester of formula 2A to the amide of formula 2 is accomplished by methods well known in the art, for example by reacting the ester directly with the amine or by using the conditions described by Basha et al in Tetrahedron Letters, (1977), p. 4171.

In step (b), the amide formed in step (a) is reacted with the halomethyl-substituted compound of formula 3 in a solvent such as THF, t-butyl methyl ether (t-BuOMe), diethyl ether (Et_2O), diglyme or a mixture thereof, preferably a mixture of THF and t-butyl methyl ether, in the presence of a strong base such as lithium diisopropylamide (LDA), lithium hexamethyldisilylamide or sodium amide, preferably LDA. The concentration of the base ranges from 2.0 to 4.0 equivalents, preferably 2.0 to 2.2 equivalents. The compound of formula 3 is reacted in a concentration range of 1.0 to 1.5 equivalents, preferably 1.1 equivalents. The reaction is carried out in a temperature range of -78°C to -20°C, preferably -50°C to -30°C.

In step (c)(i), the product of step (b) is converted to the corresponding cyano compound of formula 5a by reacting with $POCl_3$ or $SOCl_2$ in a solvent such as CH_2Cl_2 or without a solvent, preferably without a solvent. The reaction is carried out in a temperature range of 50°C to reflux, preferably at reflux.

Alternatively, in step (c)(ii), the product of step (b) or step (c)(i) is converted to the corresponding aldehyde of formula 5b by reacting with DIBALH or $LiAlH_4$ and its derivatives, preferably DIBALH, in a solvent such as toluene, THF or t-BuOMe, preferably toluene. The

reaction is carried out in a temperature range of -78°C to -30°C, preferably -78°C to -50°C.

In step (d), the product of step 5a or 5b is reacted with a piperidine derivative of formula 6 as defined above to obtain a ketone or alcohol, respectively. The reaction is carried out in a solvent such as THF, toluene or t-BuOMe, preferably THF. The concentration of the piperidine derivative ranges from 1.0 to 2.0 equivalents, preferably 1.1 to 1.2 equivalents. The reaction is carried out in a temperature range from -20°C to 50°C, preferably 35°C to 45°C, for the product of step 5a, and in a range from -78°C to 0°C, preferably -78°C to -60°C, for the product of step 5b.

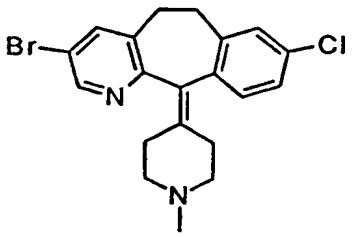
In step (e)(i), the ketone of formula 7a is cyclized to a compound of formula I wherein the dotted line represents a double bond by treatment with a strong acid such as CF_3SO_3H, CH_3SO_3H or BF_3·HF, preferably CF_3SO_3H, in a temperature range of 50°C to 120°C, preferably 90°C to 95°C.

In step (e)(ii), the alcohol of formula 7b is cyclized to a compound of formula I wherein the dotted line represents a single bond by treatment with an acid such as $H2SO_4$, polyphosphoric acid or CH_3SO_3H, preferably polyphosphoric acid, in a temperature range of 100°C to 200°C, preferably 160°C to 180°C.

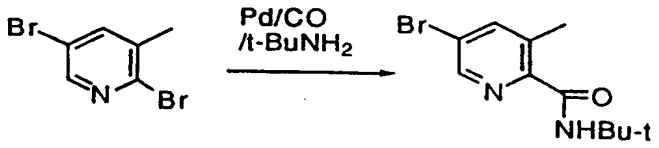
Starting materials of formula 1, 3, 6 and NHR^5R^6 are known in the art or can readily be prepared by one skilled in the art.

Following are specific examples of the procedures in the various steps of the process of this invention for preparing compounds of formula I, although those skilled in the art will appreciate that similar procedures within the scope of the process of this invention can be used to prepare other compounds of formula I.

EXAMPLE 1

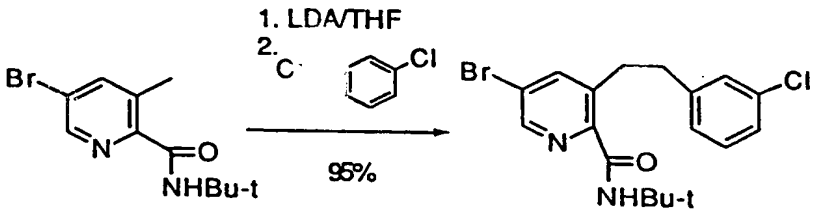


Step (a):



To an autoclave were added 16 g (60.6 mmole) of 2,5-dibromo-3-methylpyridine, 4.5 g (6.4 mmole) of $(Ph_3P)_2PdCl_2$, 150 ml of toluene, 150 ml of CH_3CN, and 17 ml (160 mmole) of t-butylamine. The autoclave was sealed, evacuated, purged with nitrogen and charged with carbon monoxide to 120 psi. The reaction mixture was heated to 60°C for two days with periodical refilling, as necessary, and then cooled to r.t. The contents of the autoclave was vented under vacuum, flushed with nitrogen and transferred to a flask with the aid of water and EtOAc. The mixture was concentrated and filtered through a pad of celite. The filtrate was extracted with EtOAc, the combined extract was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was separated by column chromatography to obtain 11 g of the product as an oil, 67 % yield. 1H NMR ($CDCl_3$): 8.40 (d, J=2.1, 1H), 7.90 (br, 1H), 7.73 (d, J=2.1, 1H), 2.73 (s, 3H), 1.48 (s, 9H). ^{13}C NMR ($CDCl_3$): 164.53, 146.58, 146.08, 142.92, 136.93, 122.28, 50.86, 28.71, 20.57.

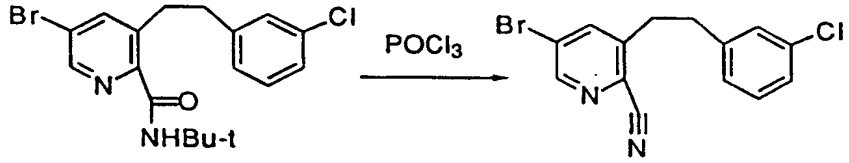
Step (b):



To a solution of 10.56 ml (80.7 mmole) of i-Pr_2NH in 90 ml THF at 0°C was added 31.20 ml (77.9 mmole) of 2.5 M n-BuLi in hexanes and

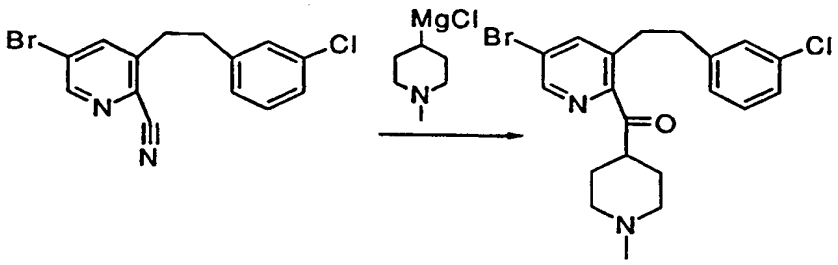
the solution was stirred for 30 min. To the LDA solution was added dropwise a solution of 9.6 g (35.4 mmole) of the product of Step (a) in 45 ml THF at -78°C. The resulting purple solution was stirred at -78°C for 30 min., at -42°C for 15 min., and then recooled to -78°C. To this solution was added dropwise a solution of 8.0 g (50 mmole) of 3-chlorobenzyl chloride in 50 ml THF. The reaction was warmed to room temperature over 1 hour. Saturated NH_4Cl solution (50 ml) and ice-water (50 ml) were added to the reaction and the mixture was evaporated to half of the volume under vaccum. Extraction with EtOAc (100 ml x 2) and evaporation of the solvent gave 16 g of the desired product, which was used directly in next step. ^1H NMR ($CDCl_3$): 8.40 (d, J=2.1, 1H), 7.78 (b, 1H), 7.55 (d, J=2.1, 1H), 7.16 (m, 3H), 7.06 (m, 1H), 3.38 (m, 2H), 2.90 (m, 2H), 1.45 (s, 9H).

Step (c)



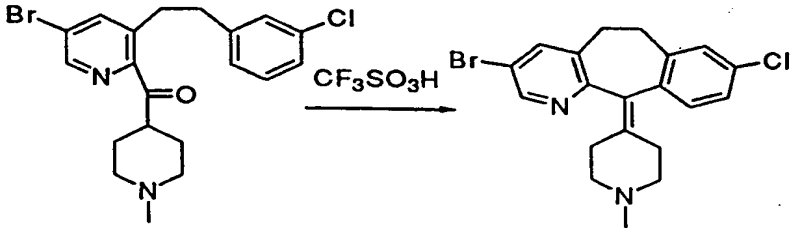
The amide (16 g) of Step (b) was dissolved in $POCl_3$ (100ml) and the solution was refluxed for 2.5 hr and then concentrated to a third of its volume under vaccum, poured into 200 g ice and adjusted to pH 8 with 50% NaOH at 25°C. The resultant mixture was stirred for 2 hr at 25°C and the pH maintained at 8 with NaOH. Extraction with EtOAc (100ml x 2) and evaporation gave a solid residue which was washed with hexane. After drying, 10 g of product was obtained; the yield was 88% in two steps. ^{1}NMR ($CDCl_3$): 8.62 (d, J=2.0, 1H), 7.71 (d, J=2.0, 1H), 7.23 (m, 2H), 7.16 (s, 1H), 7.04 (m, 1H), 3.11 (m, 2H), 2.95 (m, 2H). ^{13}C NMR ($CDCl_3$): 150.21, 142.66, 141.10, 139.97, 134.42, 131.86, 129.96, 128.54, 126.95, 126.63, 124.60, 115.63, 35.94, 34.26.

Step (d)



To a solution of the product of Step (c) (2 g, 6.25 mmole) in THF (20 ml) at 40-45°C was added dropwise N-methyl-piperidyl magnesium chloride (8 ml, 0.94 M, 1.2 eq) and the reaction mixture was stirred for 30 min. The reaction mixture was adjusted to pH 2 with 2N HCl and was stirred for 1 h. The pH was adjusted to 10 with 28% NH_4OH and the mixture was extracted with EtOAc (100ml x 2). The organic layer was separated and concentrated to give a residue, which was passed through silica gel as a CH_2Cl_2 solution. The solvent was removed to obtain an oil (2.3 g). ^1H NMR ($CDCl_3$): 8.54 (d, J=2.1, 1H), 7.62 (d, J=2.1, 1H), 7.08 (m, 3H), 7.30 (dt, J=7.0, 1.5, 1H), 3.62 (m, 1H), 3.08 (m, 2H), 2.86 (m, 4H), 2.28 (s, 3H), 2.06 (m, 2H), 1.82 (m, 2H), 1.75 (m, 2H). ^{13}C NMR ($CDCl_3$): 205.12, 150.09, 147.62, 142.81, 141.65, 139.37, 134.14, 129.69, 128.59, 126.75, 126.41, 123.17, 55.19, 46.35, 43.73, 36.97, 34.63, 27.93.

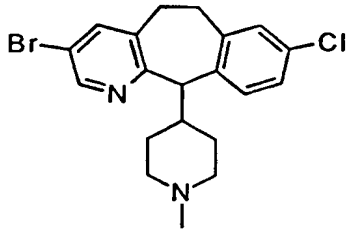
Step (e):



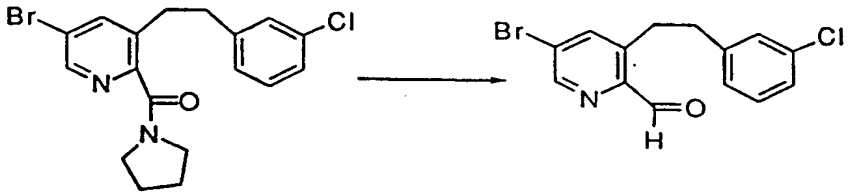
Stir a solution of ~2 g (4.6 mmole) of the product of Step (d) in 4.6 ml (50 mmole) of CF_3SO_3H at 90°C for 18 hr under nitrogen. Pour the cooled reaction into ice water and adjust to pH 10 with 29% NH_4OH. Extract the product with CH_2Cl_2 (2X) to obtain 2 g residue. Purify by chromatography on a silica gel column, eluting with CH_2Cl_2:CH_3OH: NH_4OH (28%) (100:3:0.1). The yield is 68% based on comsumption of the starting ketone.^1H NMR ($CDCl_3$): 8.44 (d, J=2.2, 1H), 7.56 (d, J=2.2,

1H), 7.12 (m, 3H), 3.36 (m, 2H), 2.70 (m, 4H), 2.50 (m. 1H), 2.35 (m. 3H), 2.25 (s, 3H), 2.05 (m, 2H). ^{13}C ($CDCl_3$): 155.79, 147.36, 139.57, 139.12, 137.45, 135.18, 132.78, 131.62, 130.64, 128.77, 126.12, 118.53, 56.74, 45.93, 31.33, 31.30, 30.99, 30.73.

EXAMPLE 2

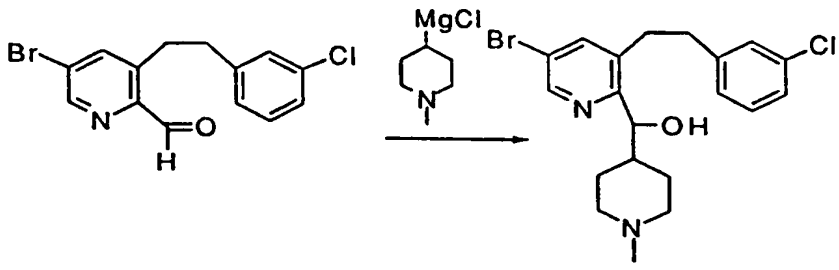


Step1:



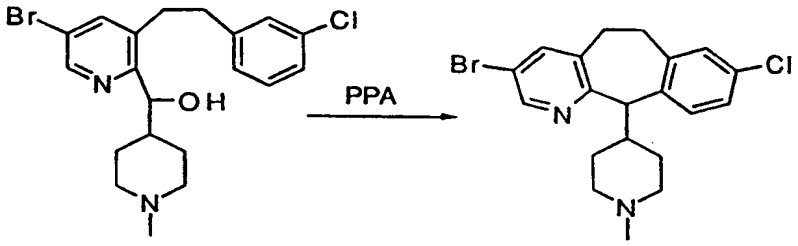
To a solution of the starting amide (8 g, 20.3 mmole) in 80 ml of toluene at -70°C was added 22 ml (22 mmole in toluene) of DIBALH dropwise over 10 min. The reaction was monitored by TLC; after completion, the reaction mixture was transferred at -60°C to a quenching solution prepared with 150 ml of water and 11 g of malic acid, with the pH being adjusted to 14 with 50% NaOH. The resultant mixture was stirred for 15 min and the toluene layer was separated. The aqueous layer was extracted with toluene (100mL), the toluene layers were combined, dried over $MgSO_4$ and filtered. Concentration gave 5.7 g product, 87% yield. ^1H NMR ($CDCl_3$): 10.10 (s, 1H), 8.71 (d, J=2.0, 1H), 7.67 (d, J=2.0, 1H), 7.10-7.20 (m, 4H), 3.25 (m, 2H), 2.85 (m, 2H).

Step 2:



To a mixture of the aldehyde of Step 1 (0.32 g, 0.60mmol) in THF (20 ml) at -78°C was added dropwise the Grignard reagent (0.9 M, 0.7 ml, 0.63 mmol). After 30 min, aqueous NH_4Cl (~2 ml) was added and the mixture was warmed to room temperature. Water (50ml) was added and the mixture was extracted with EtOAc (50ml x 2). After concentrating the combined organic phase, the residue was separated by preparative TLC to give 75 mg of product. ^1H NMR ($CDCl_3$): 8.49 (d, J=2.1, 1H), 7.66 (d, J=2.1, 1H), 7.51 (d, J=2.3, 1H), 7.05 (d, J=2.3, 1H), 4.69 (d, J=4.50, 1H), 2.70-3.10 (m, 6H), 2.19 (s, 3H), 1.80 (m, 3H), 1.55 (m, 4H), 1.35 (m, 1H).

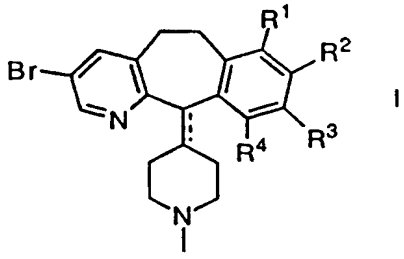
Step 3:



A mixture of 0.5 g of the alcohol from Step 2 with 5 g of polyphosphoric acid was heated to 170°C for 2 hr. Afer cooling to r.t., the reaction was adjusted to pH 12 with aqueous NaOH and extracted with EtOAc. The organic layer was combined and dried over $MgSO_4$ and concentrated to give the product. ^1H NMR ($CDCl_3$): 8.35 (d, J=2.0, 1H), 7.50 (d, 1H), 7.06 (m, 3H), 3.85 (d, J=6.3, 1H), 3.35 (m, 2H), 2.80 (m, 4H), 2.20 (s, 3H), 2.05 (m, 1H), 1.75 (m, 2H), 1.20-1.50 (m, 4H).

We Claim:

1. A process for preparing a compound of the formula I



I

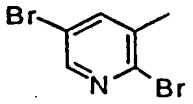
wherein:

R^1, R^2, R^3 and R^4 are independently selected from the group consisting of hydrogen and halo, provided that at least one of R^1, R^2, R^3 and R^4 is hydrogen and at least one of R^1, R^2, R^3 and R^4 is halo; and

the dotted line represents an optional double bond;

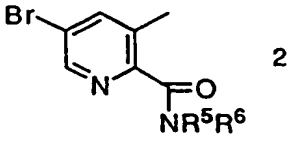
comprising:

(a) reacting a compound of formula 1



1

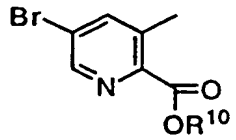
(i) with an amine of the formula NHR^5R^6, wherein R^5 is hydrogen and R^6 is C_1-C_6 alkyl, aryl or heteroaryl; R^5 is C_1-C_6 alkyl, aryl or heteroaryl and R^6 is hydrogen; R^5 and R^6 are independently selected from the group consisting of C_1-C_6 alkyl and aryl; or R^5 and R^6, together with the nitrogen to which they are attached, form a ring comprising 4 to 6 carbon atoms or comprising 3 to 5 carbon atoms and one hetero moiety selected from the group consisting of -O- and -NR^9-, wherein R^9 is H, C_1-C_6 alkyl or phenyl; in the presence of a palladium catalyst and carbon monoxide to obtain an amide of formula 2:



2

; or

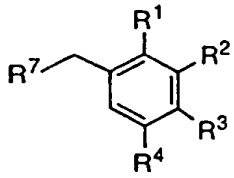
(ii) with an alcohol of the formula $R^{10}OH$, wherein R^{10} is C_1-C_6 lower alkyl or C_3-C_6 cycloalkyl, in the presence of a palladium catalyst and carbon monoxide to obtain the ester of formula 2A



2A

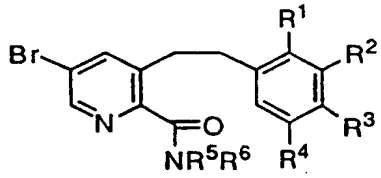
followed by reacting the compound of 2A with an amine of formula NHR^5R^6 to obtain the amide of formula 2;

(b) reacting the amide of formula 2 with a compound of formula 3



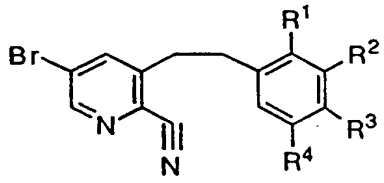
3

wherein R^1, R^2, R^3 and R^4 are as defined above and R^7 is Cl or Br, in the presence of a strong base to obtain a compound of formula 4



4

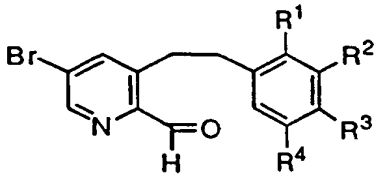
(c)(i) converting a compound of formula 4 to a cyano compound of formula 5a



5a

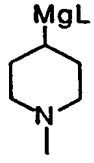
; or

(c)(ii) converting a compound of formula 4 or a cyano compound of formula 5a to an adlehyde of formula 5b



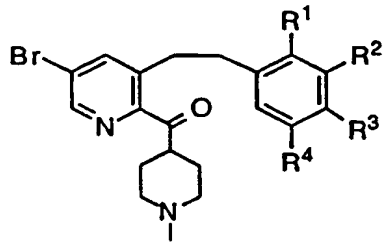
5b

(d) reacting compound 5a or 5b with a piperidine derivative of formula 6

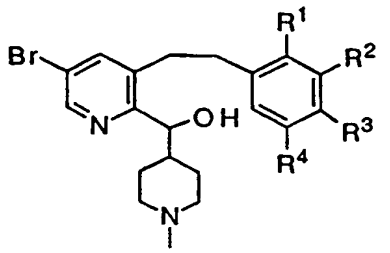


6

wherein L is a leaving group selected from the group consisting of Cl and Br, to obtain a ketone of formula 7a or an alcohol of formula 7b, respectively:



7a



7b

(e)(i) cyclizing a compound of formula 7a to obtain a compound of formula I wherein the dotted line represents a double bond; or

(e)(ii) cyclizing a compound of formula 7b to obtain a compound of formula I wherein the dotted line represents a single bond.

2. A process of claim 1 wherein R^5 is t-butylamine and R^6 is H, or R^5 and R^6 together are $-(CH_2)_4-$.

3. A process of claim 1 wherein the palladium catalyst is $Pd(OAc)_2/P(R^{10})_3$; $(PPh_3)_2PdCl_2$; $Pd(PPh_3)_4$; $(R^{10})_3P/Pd_2(dba)_3$; or Pd/C, wherein Ac is acetyl, R^{10} is C_1 to C_6 alkyl or aryl, Ph is phenyl, and dba is dibenzylidene acetone.

4. A process of claim 1 wherein R^1 and R^2 are independently selected from the group consisting of chloro and bromo, and R^3 and R^4 are each hydrogen.

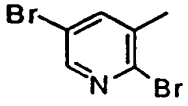
5. A process of claim 1 wherein R^2 and R^4 are independently selected from the group consisting of chloro and bromo, and R^1 and R^3 are each hydrogen.

6. A process of claim 4 wherein R^5 is t-butylamine, R^6 is H, and the palladium catalyst is $Pd(OAc)_2/P(R^{11})_3$ wherein Ac is acetyl and R^{11} is C_1 to C_6 alkyl or aryl.

7. A process of claim 5 wherein R^5 is t-butylamine, R^6 is H, and the palladium catalyst is $Pd(OAc)_2/P(R^{11})_3$ wherein Ac is acetyl and R^{11} is C_1 to C_6 alkyl or aryl.

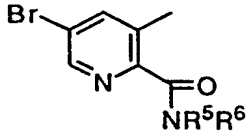
8. A process of claim 1 comprising

(a) reacting a compound of formula 1



1

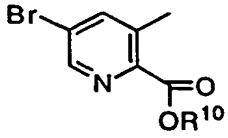
(i) with an amine of the formula NHR^5R^6, wherein R^5 and R^6 are as defined in claim 1, in the presence of a palladium catalyst and carbon monoxide to obtain an amide of formula 2:



2

; or

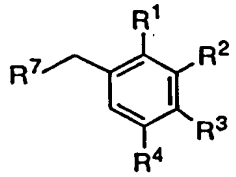
(ii) with an alcohol of the formula $R^{10}OH$, wherein R^{10} is C_1-C_6 lower alkyl or C_3-C_6 cycloalkyl, in the presence of a palladium catalyst and carbon monoxide to obtain the ester of formula 2A



2A

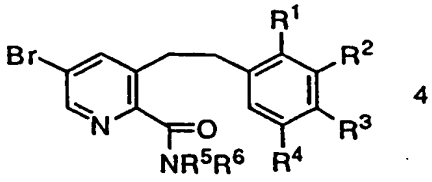
followed by reacting the compound of 2A with an amine of formula NHR^5R^6 to obtain the amide of formula 2;

(b) reacting the amide of formula 2 with a compound of formula 3



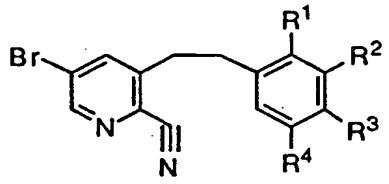
3

wherein R^1, R^2, R^3, R^4 and R^7 are as defined in claim 1, in the presence of a strong base to obtain a compound of formula 4



4

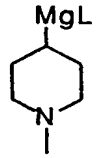
(c) converting a compound of formula 4 to a cyano compound of formula 5a



5a

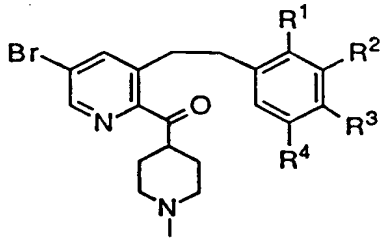
; or

(d) reacting compound 5a with a compound of formula 6



6

as defined in claim 1, to obtain a ketone of formula 7a:

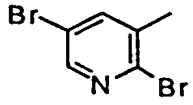


7a

(e)(i) cyclizing a compound of formula 7a to obtain a compound of formula I wherein the dotted line represents a double bond.

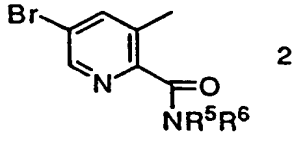
9. A process of claim 1 comprising:

(a) reacting a compound of formula 1



1

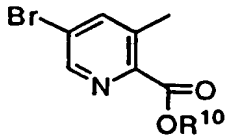
(i) with an amine of the formula NHR^5R^6, wherein R^5 and R^6 are as defined in claim 1, in the presence of a palladium catalyst and carbon monoxide to obtain an amide of formula 2:



2

; or

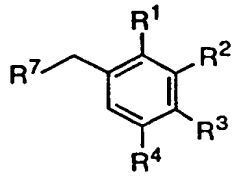
(ii) with an alcohol of the formula $R^{10}OH$, wherein R^{10} is C_1-C_6 lower alkyl or C_3-C_6 cycloalkyl, in the presence of a palladium catalyst and carbon monoxide to obtain the ester of formula 2A



2A

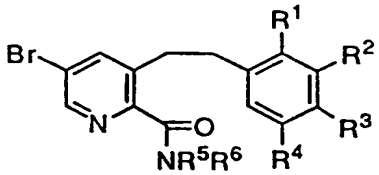
followed by reacting the compound of 2A with an amine of formula NHR^5R^6 to obtain the amide of formula 2;

(b) reacting the amide of formula 2 with a compound of formula 3



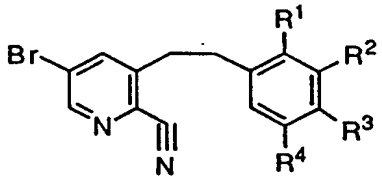
3

wherein R^1, R^2, R^3, R^4 and R^7 are as defined in claim 1, in the presence of a strong base to obtain a compound of formula 4



4

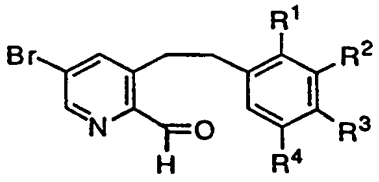
(c)(i) converting a compound of formula 4 to a cyano compound of formula 5a



5a

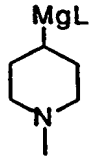
; or

(c)(ii) converting a compound of formula 4 or a cyano compound of formula 5a to an adlehyde of formula 5b



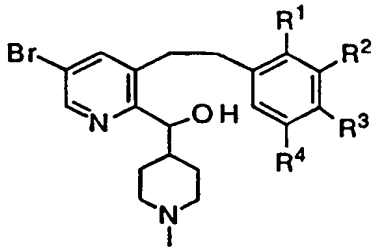
5b

(d) reacting compound 5b with a compound of formula 6



6

as defined in claim 1, to obtain an alcohol of formula 7b:



7b

(e)(ii) cyclizing a compound of formula 7b to obtain a compound of formula I wherein the dotted line represents a single bond.

INTERN ' TIONAL SEARCH REPORT

ational Application No
PCT/US 98/11403

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 151 423 A (J. J. PIWINSKI ET AL.) 29 September 1992 cited in the application see column 24, line 5 - column 26, line 42 see column 48, line 24 - column 49, line 36	1,8,9
A	WO 95 10516 A (SCHERING CORP.) 20 April 1995 see page 49, line 6 - page 51, line 7 see page 61, line 11 - page 64, line 6	1,8,9
A	WO 95 10515 A (SCHERING CORP.) 20 April 1995 see page 41, line 6 - page 43, line 7 see page 53, line 6 - page 55, line 23	1,8,9

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 August 1998	03/09/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hass, C

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INTERNATIONAL SEARCH REPORT

...rmation on patent family members

)ational Application No
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/11403

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO 97 23478 A (SCHERING CORP.) 3 July 1997 cited in the application see abstract	1

1

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